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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/600,900 | 06/20/2003 | Gary W. Blissard | BTI-47CON | 5915 |

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EXAMINER

GUZO, DAVID

ART UNIT PAPER NUMBER

1636

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/600,900

Applicant(s)

BLISSARD ET AL.

Examiner

David Guzo

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>6/20/03</u> | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering recombinant or foreign polynucleotides to mammalian cells *in vitro*, and a method for expressing proteins of interest in mammalian cells *in vitro*, said methods using a genetically engineered baculovirus comprising a heterologous envelope protein or molecule that facilitates entry of the virus into cells not normally a host for the baculovirus, does not reasonably provide enablement for a method of administering gene therapy or expressing foreign or heterologous polynucleotides in mammalian cells *in vivo*, said methods using a genetically engineered baculovirus comprising any heterologous (non-envelope) protein or other molecule that facilitates entry of the baculovirus into a target mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant claims a method for administering gene therapy (or expressing a recombinant or foreign protein *in vivo* or *in vitro*) comprising administering recombinant baculoviral vectors comprising heterologous proteins such as the VSV G glycoprotein. The instant baculoviral expression system is contemplated for *in vitro* and *in vivo* uses. The *in vivo* uses are for delivery of gene therapy agents. As the only *in vivo* uses

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contemplated by applicant involve gene therapy, the claims will be evaluated as reading on gene therapy.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

1) Unpredictability of the art. The gene therapy art is extremely unpredictable. This unpredictability is manifested at practically every level of gene therapy, from the design of the vector, manufacture of the vector, delivery of the vector to the proper target cells or tissues *in vivo*, transient or inefficient expression of the transgene in cells *in vivo*, etc. While some studies indicate that pseudotyped and non-pseudotyped recombinant baculoviral vectors can transduce some mammalian cells *in vitro* and *in vivo* (in mice) and express marker genes in said cells, the ability of baculoviruses to effectively target the appropriate cells or tissue *in vivo*, infect and express transgenes in mammalian cells at therapeutic levels and for a sustained period under *in vivo* conditions is unknown. Inactivation of baculoviral vectors by the mammalian complement system has been a significant problem with regard to use of baculoviral vectors *in vivo*. While applicants' invention could possibly reduce the complement mediated inactivation of baculoviruses

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by removing the gp64 envelope protein (possibly the site of complement attack) and pseudotyping the viruses with proteins (i.e. VSV G protein) which are not as efficient in activating the complement pathway, this has not been tested *in vivo* in any experiment involving administration of baculoviral gene therapy vectors to humans. Indeed, no clinical experience using recombinant baculoviral vectors as gene therapy agents has been accumulated and their ability to function as gene therapy vectors in humans is unknown.

Indeed, art published well after the filing date of applicants' invention indicates that while recombinant baculoviral vectors have some promise as gene therapy vectors, considerable further research needs to be conducted with regard to what promoters are effective for expression of transgenes *in vivo*, how much, if any, of the viral genome is maintained in target cells and for how long, whether the baculoviral nucleic acid is integrated into the host genome and other basic molecular biology questions which need to be answered before baculoviral vectors can even be considered for gene therapy (See Loser et al., *Current Gene Therapy*, 2002, Vol. 2, pp. 161-171 and Ghosh et al., *Molecular Therapy*, 2002, Vol. 6, No. 1, pp. 5-11).

For reviews of the gene therapy art overall, see Anderson, *Nature*, Vol. 392, 1998, pp. 25-30; Verma et al., *Nature*, Vol. 389, 1997, pp. 239-242; Mountain, TIBTECH, Vol. 18, 2000, pp. 119-128; Kmiec, *American Scientist*, Vol. 87, 1999, pp. 240-247, Juengst, *BMJ*, 2003, Vol. 326, pp. 1410-1411, etc.).

With regard to the *in vivo* use of heterologous envelope (or non-envelope) proteins or other (non-protein) molecules to generate recombinant baculoviruses

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wherein the non-envelope proteins or other molecules facilitate entry of the virus into target cells not normally infected by the non-recombinant baculovirus, the art is highly unpredictable. Indeed, even in the recombinant retroviral vector art, where pseudotyping of viral particles has been most advanced, the ability of pseudotyped viral particles to infect the intended target cells *in vivo* is highly unpredictable. This unpredictability involves possible improper folding of the heterologous envelope protein, poor incorporation of the heterologous protein on the envelope surface, failure of the heterologous protein to trigger fusion with the host membrane, etc. (See Paillard, Human Gene Therapy, 1998, Vol. 9, pp. 767-770). Also, Paillard notes that while pseudotyped viral vectors can often infect target cells *in vitro*, they are often not predictably able to infect the same cells in an *in vivo* environment.

In the instant case, applicants are claiming a method of delivering gene therapy by administering recombinant baculoviruses comprising chimeric envelopes containing proteins or other non-protein molecules which are not normally even expressed on envelopes. It is totally unpredictable whether a protein which facilitates entry into target cells of a non-enveloped virus (i.e. a protein expressed on a viral capsid surface) would fold properly and maintain its' functions in a totally different environment (e.g. on envelope surface of a different virus) in the context of a gene therapy vector *in vivo*.

2) State of the art. The art at the time the instant invention was made was nil, with no demonstrated unambiguous successes in treating any disease in humans. With regard to baculoviral vectors, no clinical experience has been accumulated.

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- 3) Number of working examples. Applicant presents no working examples of the claimed invention.
- 4) Amount of guidance presented in the specification. Applicant presents no guidance on how the skilled artisan would practice successful gene therapy using the claimed pseudotyped baculoviral vectors. Applicant presents no guidance on how the skilled artisan would address and overcome the art recognized problems (recited above) associated with successful practicing of gene therapy in patients.
- 5) Scope of the claims. The claims are broad with the claims reciting a method of administering any gene therapy treatment (for any disease) in any mammal.
- 6) Nature of the invention. The invention involves one of the most complex and unpredictable areas of medicine/molecular biology; gene therapy.
- 7) Level of skill in the art. The level of skill in the gene therapy art is high; however, as noted by some of the preeminent researchers in gene therapy (i.e. W. French Anderson, I. M. Verma, etc.), significant hurdles remain to be overcome in order for the skilled artisan to practice successful gene therapy.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Blissard et al.

Both applicants and Blissard et al. (U.S. Patent 5,750,383, issued 5/12/98, see whole document, particularly Fig. 4 and the paragraph bridging Columns 2-3, Column 4, lines 13-60 and Column 12, lines 12-58) recite a method of protein expression comprising construction of a genetically engineered baculovirus comprising a deleted gp64 envelope protein and wherein said baculovirus can comprise a heterologous envelope protein obtained from a cell engineered to express said envelope protein or the baculovirus can be further engineered to express an envelope protein from another virus (such as the gp64 envelope protein from a different baculovirus). Specifically, Blissard et al. recites that gp64null baculoviruses can be rescued by recombination with a plasmid comprising a gp64 gene (which can be from the same or a different baculovirus) and optionally a foreign gene of interest. The resultant pseudotyped baculovirus can be delivered to a suitable cell and used to express the foreign gene in said cells. With regard to the pseudotyped baculovirus being able to infect cells not normally used as hosts of the progenitor (original non-pseudotyped) baculovirus, the choice of the heterologous baculovirus gp64 gene will alter the host range of the recombinant virus since this envelope protein is involved in the attachment to and infection of host cells. For example, if the AcMNPV gp64 protein is expressed by a gp64 null OpMNPV virus, the resultant viruses will more efficiently enter host cells which are not normally host cells of the OpMNPV because the AcMNPV, as a result of it's

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gp64 envelope protein, is able to enter and replicate in a broader range of host cells.

Alternatively, if the OpMNPV gp64 gene is expressed by AcMNPV gp64 null viruses, the resultant recombinant baculovirus will be more specific to a narrower range of host cell types. Blissard et al. therefore teaches the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 (and dependent claim 9) is vague in that the claim recites the "genetically engineered baculovirus of claim 1"; however, claim 1 is a method claim which recites creating a first genetically engineered baculovirus in step (a) and in step (b) further modifying said engineered baculovirus to express a gene therapy agent or recombinant polynucleotide. It is unclear what genetically engineered baculovirus is being referred to, i.e. the baculovirus recited in step (a) or the further modified baculovirus of step (b)?

Miscellaneous:

In Claim 1, line 9, baculovirus is misspelled as "baculoviru"

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, PhD., whose telephone number is (571)


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272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
March 29, 2004


DAVID GUZO
PRIMARY EXAMINER